CHAPTER 28

Jaundice

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Jaundice (icterus) is a yellowing of the skin, sclerae, and mucous membranes resulting from elevated circulating bilirubin from the breakdown of hemoglobin. Mild elevation in the serum bilirubin (2 to 2.5 mg/dL) is first noted as mild jaundice when the sclerae are viewed in natural light. Yellow skin coloring also occurs with elevated serum carotene, but the sclerae will be anicteric.

Hyperbilirubinemia can be divided into unconjugated (indirect) and conjugated (direct) types. The unconjugated type occurs from overproduction of bilirubin or defects in liver uptake or conjugation (hemolysis, ineffective erythropoiesis, or Gilbert syndrome). The conjugated type occurs from intra- or extrahepatic cholestasis, resulting in decreased excretion of conjugated bilirubin. An unconjugated hyperbilirubinemia occurs when the indirect fraction is 85% of the total. A conjugated hyperbilirubinemia occurs when the direct fraction is more than 30% of the total measured bilirubin.

Because jaundice is a symptom and not a specific disorder, it is important to identify its etiology, and then to identify any treatment that may be indicated. It is always important to obtain a complete history, and with the workup of jaundice this may provide important clues to the etiology.

GALLBLADDER DISEASE OR OBSTRUCTIVE JAUNDICE

Gallstones are the most common cause of blocked bile ducts and cancer is a much less common cause, but together these are the most common extrahepatic etiologies of jaundice. Stones typically form in the gallbladder (cholelithiasis) and can block the common bile duct (choledocholithiasis). Obstruction of the biliary system causes cholestasis or "obstructive jaundice" and may lead to cholecystitis, or inflammation of the gallbladder.

Symptoms

- Abdominal pain
- Jaundice
- Loss of appetite (anorexia)
- Weight loss
- Pruritus
- Dark urine

- Pale stools
- Vomiting
- Fever

Signs

- Xanthelasmas
- Murphy's sign—Pain with palpation of right upper quadrant on exhalation in the setting of cholecystitis

Workup

- Alkaline phosphatase and gamma-glutamyl transpeptidase (GGT)—Both increase disproportionately with cholestasis
- LFTs—May be markedly elevated with a common duct stone
- Ultrasound—Good screening tool for biliary tree dilation and gallstone identification; may also detect parenchymal disease
- CT—Best for evaluation of parenchymal liver disease; also good for evaluating the pancreas; can evaluate for biliary tree dilation
- ERCP—Dye is instilled into the biliary tree and is most useful after initial screening with ultrasound (US), CT, or MRI in the identification of biliary abnormalities; good for evaluating intraductal stones; provides direct visualization of the biliary tree; useful for extra hepatic obstruction.
- MRI imaging of the biliary tree may detect stones or ductal lesions and is a noninvasive alternative to ERCP.
- Consider liver biopsy.

Comments and Treatment Considerations

There is a risk of nutritional deficiencies and fat malabsorption. For diarrhea, a trial of a low-fat diet can be considered. Patients with steatorrhea may have a deficiency in the fat-soluble vitamins (A, D, E, K). Gallstones that are impacted require either endoscopic removal or cholecystectomy.

ERCP can be used to remove stones, perform papillotomy, or to place stents or drainage catheters to improve bile flow, for symptomatic choledocholithiasis. Percutaneous transhepatic biliary drainage can be tried if ERCP fails.

Cholecystectomy should be considered for symptomatic gallstone disease. Chemotherapy may be tried in the case of biliary tract tumors. Pruritus may be treated with cholestyramine, a bile acid sequestrant resin, at a dose of 4 g mixed with water before meals.

Monitor for osteoporosis in patients with cholestatic liver disease, supplement calcium, and vitamin D and screen with bone densitometry.

GILBERT SYNDROME

Gilbert syndrome is a common, hereditary, mild disorder of the liver. In this syndrome the liver improperly processes bilirubin produced from the breakdown of RBCs. There is decreased activity of the enzyme UDP glucuronosyltransferase, which causes an increase in the indirect fraction of serum bilirubin.

Approximately 3% to 10% of the U.S. population have Gilbert syndrome, with men affected more than women (2 to 7:1). Most often people discover that they have Gilbert syndrome when routine blood testing reveals elevated unconjugated hyperbilirubinemia with other liver function values unaffected.

Jaundice or increased bilirubin levels may occur or become more pronounced during periods of stress or illness. The condition is benign and typically does not require any treatment. There is no indication for liver biopsy.

Symptoms
- May have mild jaundice, especially of sclera

Signs
- Elevated indirect bilirubin ++++

Workup
- LFTs normal ++++
- No signs of hemolysis ++++
- No biopsy indicated ++++
- Important to rule out other causes of elevated serum bilirubin

Comments and Treatment Considerations
It is normally a benign condition with excellent prognosis, and usually no treatment is indicated. Jaundice or bilirubin level may increase with illness or stress (transient).

HEMOLYSIS

RBCs typically have a life span of 120 days. When they are destroyed prematurely it is called hemolysis. The bone marrow typically reacts by increasing the production of red cells to prevent the development of anemia. If the production cannot keep up with the rate of destruction, anemia develops. The symptoms of hemolytic anemia vary according to the speed at which the anemia develops. If the anemia is mild or develops slowly, the patient may remain asymptomatic. If the process is more moderate the patient may complain of dyspnea with exertion. The possible etiologies include spherocytosis, G6PD deficiency, sickle cell disease, microangiopathic hemolytic anemia, autoimmune disorders, and drugs.

Symptoms
- Jaundice—Usually mild
- Fatigue
- Weakness
- Dizziness
- Diaphoresis
- Dyspnea
- Chest pain
- Leg cramps with exercise
- Abdominal fullness or discomfort

Signs
- Jaundice
- Pallor
- Tachycardia
- Tachypnea
- Hypotension
- Splenomegaly

Workup
- Bilirubin level—Usually only mildly elevated (3 to 5 mg/dL); may be within normal range if mild
- LDH elevated with hemolysis
- CBC—Evaluate for schistocytes (fractured RBCs) and reticulocyte count; CBC usually increased; indicates increased erythropoiesis
- Direct antiglobulin test (DAT; direct Coombs' test) to detect the presence of IgG and complement (C3) on the RBCs; differentiates immune from nonimmune hemolysis
- LFTs and alkaline phosphatase usually within normal limits
- Haptoglobin levels are decreased as protein binds hemoglobin.
- Urinalysis—Elevated urobilinogen, even without hyperbilirubinemia

Comments and Treatment Considerations
For mild symptoms no treatment may be needed. Monitor hemoglobin and the potential for transfusion. For more advanced symptoms, a steroid such as prednisone is the treatment of choice. Doses are usually started high and then followed by a gradual taper over months.

For patients with an inadequate response to steroids, splenectomy may be an option. If symptoms continue after splenectomy, immunosuppressive therapy may be indicated with cyclophosphamide or azathioprine. Plasmapheresis is another option.

HEPATITIS

Hepatitis is an inflammation of the liver with hepatocellular necrosis that results most commonly from viral infection, alcoholism, toxins, or autoimmune disorders. Inflammation within the liver is the most common intrahepatic cause of jaundice. The manifestations vary depending on whether the clinical scenario is acute or chronic. When considering the potential etiologies, it is important to assess the risk factors (foreign travel, alcoholism, history of IV drug use, blood transfusions before 1992, high-risk sexual behavior, hemodialysis, raw seafood ingestion, tattoos or body piercing, needle punctures, or close contact with infected individual). Both viral- and toxin-induced hepatitis may lead to fulminant hepatic failure, chronic liver disease or end-stage liver disease (ESLD). In the United States more than 50% of ESLD results from alcoholism.

Symptoms
- Jaundice ++++
- Abdominal pain +++
- Nausea +++

- Emesis (nausea and vomiting preceding jaundice may indicate hepatitis or common bile duct obstruction)
- Anorexia (loss of appetite)
- Fever
- Fatigue
- Malaise
- Diarrhea
- Headache
- Dark urine ++++
- Joint pain
- Depression
- Altered taste
- Pruritus ++++

Signs

- Jaundice +++++
- Spider angiomas*
- Bruising
- Gynecomastia*
- Palmar erythema*
- Ascites*
- Testicular atrophy*
- Caput medusae*
- Hepatomegaly
- Splenomegaly
- Tenderness of liver to palpation

Workup

- Bilirubin (direct and indirect)—To determine conjugated or unconjugated, direct fraction of 30% or higher consistent with viral hepatitis, persistent elevation of total bilirubin greater than 20 mg/dL indicates poor prognosis
- Serum transaminase levels (LFTs): aspartate transaminase (AST) or serum glutamic-oxalo-acetic transaminase (SGOT), alanine transaminase (ALT) or serum glutamate pyruvate transaminase (SGPT), GGT—markers of hepatocellular injury, elevations suggestive of hepatitis (less helpful in chronic disease, because may be normal or mildly elevated), acute viral hepatitis causes LFTs to rise from several hundred to several thousand units per liter, with the AST:ALT ratio less than 1; in alcohol-induced hepatitis the AST greater than ALT, often a 2:1 ratio
- Serum alkaline phosphatase: If elevated more than threefold, consider cholestasis rather than hepatocellular process
- Hepatitis A IgM, hepatitis B surface antigen and core antibody, hepatitis C antibody
- Low albumin with high globulin level indicates chronic rather than acute liver disease.
- Prothrombin time (PT) or partial thromboplastin time (PTT) may be elevated in chronic hepatitis; prolonged PT indicates poor prognosis.

*Signs of portal hypertension or endocrine findings usually indicate chronic process.

- CBC may have a lymphocytosis with viral hepatitis; anemia may indicate GI bleeding or hemolysis
- Urinalysis—If positive for bilirubin, indicates conjugated bilirubinemia (water soluble)
- Viral hepatitis panel—Serologies including hepatitis A IgM, hepatitis B surface antigen and core antibody, and hepatitis C ribonucleic acid (RNA)
- Toxicology screen—Acetaminophen level
- Ceruplasmin (consider in patient <40 years of age)
- US—Good first test; inexpensive, quick and easy; no radiation; safe in pregnancy
- CT—Good for identifying infiltrative process (i.e., metastatic disease, but less helpful for evaluating hepatocellular disorders [too nonspecific])
- Liver biopsy—For evaluating liver architecture and determining prognosis; may also aid in diagnosis
- Differential diagnosis—Alcohol-induced hepatitis, toxin-induced hepatitis, mononucleosis, cholecystitis, ascending cholangitis, lymphoma, sarcoidosis, metastatic liver disease, pancreatic or biliary tumors

Comments and Treatment Considerations

Patients with any of the following symptoms should be considered for admission to the hospital: age more than 45, encephalopathy, vomiting, hypoglycemia, immunosuppression, volume depletion, electrolyte abnormalities, and coagulopathy. Treatment is generally supportive with IV fluids, correction of hypoglycemia, electrolyte abnormalities, and coagulopathies. Patients should abstain from alcohol and potentially hepatotoxic medications, and vaccinations should be updated.

Hepatitis A—Fecal-oral transmission. There is no treatment. Avoid alcohol because it can worsen liver disease. Hepatitis A vaccine is recommended for all children older than 2 years and anyone at risk (travel, exposure, men who have sex with men, drug abusers, recipients of clotting factor replacement, immunocompromised, chronic liver disease). Practice handwashing and careful food handling.

Hepatitis B—Generally acquired percutaneously via exposure to infected blood or body fluids. Often subclinical, but in symptomatic patients may be severe and protracted. Chronic HBV occurs in 6% to 10% and may cause cirrhosis, ESLD, and hepatocellular carcinoma (HCC). Antiviral treatment may be effective in up to 40% of patients with chronic infection. Regular medical surveillance is recommended, and liver transplant if indicated (availability issues). Avoid alcohol.

Hepatitis C—Most common of all blood infections in the United States may be contracted parenterally, sexually, or perinatally. Most patients are asymptomatic, but 85% become chronically infected. As much as 70% of chronic HCV progress to cirrhosis and ESLD, with an increased risk of HCC. Chronic infection may respond to interferon, pegylated interferon, or ribavirin. Combination therapy may eliminate the virus in 50% of patients with genotype 1. Vaccinate against hepatitis A or B, and avoid alcohol.

NEONATAL JAUNDICE

Neonatal jaundice is the most commonly encountered medical condition during the care of term, healthy newborns. Fortunately, neonatal unconjugated hyperbilirubinemia is most commonly a transitional physiologic condition that resolves without the need for medical treatment. Physiologic jaundice is caused by a combination of factors including increased turnover of fetal erythrocytes (due to higher erythrocyte mass and shortened life span of fetal erythrocytes), and decreased hepatic excretory capability due to low levels of ligandin in hepatocytes and low activity of bilirubin-conjugating enzyme glucuronyltransferase. In physiologic jaundice, total serum bilirubin levels peak at a level of 5 to 6 mg/dL on the third to fourth day of life and then declines over the first week after birth.

Pathologic jaundice should be suspected when jaundice occurs within the first 24 hours of life, with rapidly rising levels of total serum bilirubin concentration (more than 5 mg/dL increase per day), with total serum bilirubin levels higher than 17 in a full-term newborn, and with direct-reacting conjugated hyperbilirubinemia or jaundice that persists beyond 3 weeks of life. Causes of pathologic jaundice can be classified in the following manner:

UNCONJUGATED HYPERBILIRUBINEMIA

- Increased bilirubin load
  - Hemolytic causes
    - G6PD deficiency
    - Rh factor incompatibility
    - ABO incompatibility
    - Spherocytosis
  - Nonhemolytic causes
    - Cephalhematoma
    - Bruising
    - CNS hemorrhage
    - Polycythemia
    - Twin-twin transfusion
- Decreased bilirubin conjugation and clearance
  - Crigler-Najjar syndrome, types 1 and 2
  - Gilbert syndrome
  - Hypothyroidism
  - Breast milk jaundice

CONJUGATED HYPERBILIRUBINEMIA

- Biliary obstruction or cholestasis
  - Biliary atresia
  - Choledochal cyst

- Hepatocellular injury
  - Intravenous hyperalimentation
  - Viral infection (cytomegalovirus, hepatitis B)
  - Septicemia
  - α-1 Antitrypsin deficiency
  - Dubin-Johnson syndrome
  - Rotor syndrome

In very rare instances elevated bilirubin levels may lead to acute bilirubin encephalopathy or kernicterus. This condition occurs when neurotoxic unconjugated bilirubin is deposited into brain tissue. Bilirubin is bound to albumin during transport in the plasma.

When unconjugated bilirubin levels exceed the binding capacity of albumin, unbound bilirubin can more readily cross the intact blood-brain barrier. Albumin binding of bilirubin is also impaired in ill infants. There are several phases of bilirubin encephalopathy including intermediate, advanced, and chronic phases. Once it has progressed to the advanced phase, irreversible CNS damage has likely occurred.

Symptoms

- Jaundice or yellow discoloration of the skin ++++
- Yellow staining of the sclera +++++
- Poor feeding, lethargy, high-pitched cry, and decreased tone may be seen with acute bilirubin encephalopathy or kernicterus.
- Pathologic causes may present with specific symptoms such as lethargy and fever in a septic newborn, or decreased voiding and stooling with significant dehydration.

Signs

- Jaundice starts on the face and progresses in a cephalocaudal direction. ++++
- Icteric sclera +++++
- Excessive weight loss may occur with inadequate feeding and dehydration.
- Kernicterus or acute bilirubin encephalopathy can present with the following signs:
  - Early phase—Lethargy, poor suck, hypotonia
  - Intermediate phase—Moderate stupor, irritability, hypertonia, fever, high-pitched cry, retrocollis (backward arching of the neck), opisthotonos (backward arching of the trunk)
  - Advanced phase—Pronounced retrocollis-opisthotonos, shrill cry, no feeding, apnea, fever, deep stupor or coma, seizures, death
  - Chronic form—Athetoid cerebral palsy, auditory dysfunction, dental-enamel dysplasia, paralysis of upward gaze, mild intellectual deficit
  - Other signs are largely dependent on the cause. Observe for signs of possible causes of pathologic jaundice such as pallor, hepatosplenomegaly, dehydration, cephalhematoma, lethargy.

Workup

- Nonivasive transcutaneous bilirubinometry (TcB) can be used in mild jaundice to ensure that levels are safely below those requiring intervention. TcB is accurate to within 2 to 3 mg/dL of the total serum bilirubin (TSB) particularly for TSB levels less than 15 mg/dL. TcB cannot be used to monitor infants undergoing phototherapy because phototherapy "bleaches" the skin.
- Capillary total serum bilirubin and direct bilirubin levels should be ordered if TcB levels are elevated. A conjugated hyperbilirubinemia is present if the direct bilirubin level is more than 20% of the TSB. Always interpret TcB/TSB levels based on the infant's age in hours.
- Blood type (ABO, Rh)
- Direct antibody test (Coombs')
- Serum albumin
- CBC with differential
- If history or presentation suggests hemolysis, order reticulocyte count and smear for RBC morphology.
- If history or presentation suggests sepsis, perform septic workup.
- Other tests may be warranted based on history and presentation including urine for reducing substances (for galactosemia), LFTs and ultrasound (for cholestasis), thyroid function tests (for hypothyroidism), TORCH titers (for congenital infections).

Comments and Treatment Considerations

Intensive phototherapy should be initiated based upon the TSB level interpreted according to the infant's age in hours. Intensive phototherapy should be used when the TSB exceeds the line indicated for each category. Phototherapy causes a rapid configurational isomerization that changes the bilirubin isomer to a water-soluble isomer and does not allow it to cross the blood-brain barrier.

Phototherapy is most effective when more of the infant's body surface area is exposed to the phototherapy unit. Adverse effects may include insensible water loss (not as relevant as previously thought), risk of retinopathy (routine eye patches help prevent this), and decreased parental bonding time. Monitor TSB levels every 6 to 12 hours in moderate jaundice. Phototherapy is discontinued once the TSB level is less than 13 to 14 mg/dL. A follow-up TSB level measured 6 to 24 hours after discontinuation of phototherapy may be ordered to assess for rebound.

Poor response to phototherapy strongly suggests the presence of hemolysis. Exchange transfusion should be considered in infants when TSB levels rise 5 mg/dL or more above the lines (guidelines for exchange transfusion) or if the TSB rises to these levels despite intensive phototherapy. It should also be considered if there are clinical signs of acute bilirubin encephalopathy.

Bilirubin/albumin ratios can be used in conjunction with TSB levels in determining whether to perform an exchange transfusion. Exchange transfusion should only be performed by experienced personnel in a neonatal intensive care unit with full monitoring and resuscitation capabilities. Significant morbidity (apnea, bradycardia,

cyanosis, vasospasm, thrombosis, necrotizing enterocolitis) occurs in as many as 5% of exchange transfusions. Risks associated with use of blood products must also be considered.

IVIg (0.5 to 1 g/kg over 2 hours) can be administered in isoimmune hemolytic disease if intensive phototherapy is ineffective and the TSB is approaching 2 to 3 mg/dL of the exchange level. The dose can be repeated in 12 hours. IVIg has been shown to reduce the need for exchange transfusion in Rh and ABO hemolytic disease.

Hydration with IV fluid is only indicated when there is clinical evidence of dehydration. No evidence exists to show that excessive hydration affects TSB level. The best approach is to have infant breastfeed or bottle-feed (formula or expressed breast milk) every 2 to 3 hours.

Treat any underlying pathologic cause of jaundice as indicated. Empiric antibiotic therapy should be initiated once neonatal sepsis is suspected. Home phototherapy should only be used when an infant's TSB level is in an "optional" range. It is not appropriate for infants in whom serial TSB levels should be followed more regularly. Sunlight exposure should no longer be recommended because it is unsafe to expose an unclothed infant to the sun and risk sunburn or overheating.

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